Docket No.: ARO7828USA
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Mary Southam et al.

U.S. Application No.: 09/781,041

U.S. Patent No. 6,425,892

Filed: February 9, 2001 (Issued: July 30, 2002)

For: DEVICE FOR TRANSDERMAL ELECTROTRANSPORT DELIVERY OF FENTANYL AND SUFENTANIL

TRANSMITTAL LETTER

Mail Stop Hatch-Waxman PTE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Enclosed are the following items for filing in connection with the above-referenced Patent Application:

1. Request for Reconsideration of Final Determination.

A Petition for Extension of Time under 37 C.F.R. § 1.136(a) for the five month extension of time was secured on July 9, 2008.

Dated: August 18, 2008

Respectfully submitted,

By _____

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REQUEST FOR RECONSIDERATION
OF FINAL DETERMINATION

Sir:

On January 16, 2008, the United States Patent and Trademark Office ("PTO") issued a Notice of Final Determination (the "Notice") finding that U.S. Patent No. 6,425,892 ("the '892 patent") is not eligible for patent term extension under 35 U.S.C. § 156 based upon the Food and Drug Administration ("FDA") approval of IONSYS™ (fentanyl iontophoretic transdermal system).

The PTO rejected ALZA Corporation's ("Alza") patent term extension application based on the first permitted commercial marketing requirement of section 156(a)(5)(A), which limits patent term extensions to the first permitted commercial marketing or use of a drug product. The PTO concluded that the "product" in IONSYS™ is the same as the "product" in DURAGESIC® (fentanyl transdermal system), a prior approved drug, for purposes of patent term extension under section 156. The active ingredient in DURAGESIC® is fentanyl formulated as a base. The approved IONSYS™ product contains a reservoir of fentanyl hydrochloride. The PTO concluded that for purposes of section 156(a), the approved "product," is fentanyl and any salt or ester of fentanyl. Consequently, the PTO concluded that because the approved "product" in IONSYS™ had already been approved as part of the DURAGESIC® new drug application ("NDA"), the later IONSYS™ system does not represent the first commercial marketing or use of the "product" under the provision of law under which the regulatory review occurred. Notice at 2-3.

It is respectfully submitted that the PTO applied the wrong legal standard in denying the application for term extension of the '892 patent. The PTO misinterpreted and misapplied both Federal Circuit law and the statutory provisions of section 156. Under the binding precedent in the Federal Circuit, the '892 patent is certainly eligible for term extension.

Moreover, even under the legal standard that the PTO did apply, the patent term extension of the '892 patent should have been granted, for two reasons. First, the PTO's Notice of Final Determination failed to take into account the process of delivery of the IONSYS™ system, which makes clear that the delivered moiety is protonated fentanyl. Protonated fentanyl is not a salt or ester of fentanyl, and has not already received regulatory approval. Thus, even under the PTO's definition of "product" for purposes of patent term extension under section 156, the '892 patent is eligible for extension.

Second, the IONSYS™ system is a drug-device combination product that represents an innovation in the delivery of palliative care to patients. FDA approved the IONSYS™ system only after years of careful review of the entire system. This new product development is precisely what Congress meant to encourage with the passage of the Hatch-Waxman amendments to the Federal Food, Drug, and Cosmetic Act ("FDCA") in general, and

the patent term extension provision, in particular.[1] Even under the legal standard espoused by the PTO, the term extension for the '892 patent should have been granted.

In view of these reasons, the '892 patent in connection with IONSYS™ (fentanyl iontophoretic transdermal system) should be eligible for patent term restoration under 35 U.S.C. § 156.

I. Background

IONSYS™ is a patient-controlled iontophoretic transdermal system with fentanyl hydrochloride for providing on-demand systemic delivery of fentanyl, an opiod agonist, for up to 24 hours or a maximum of 80 doses, whichever comes first. Alza submitted NDA 21-338 to FDA for IONSYS™ on September 23, 2003 under section 505(b)(1) of the FDCA, and FDA approved IONSYS™ for commercial use and sale on May 23, 2006. Alza then timely applied for an extension of the patent term of the '892 patent under 35 U.S.C. § 156 on July 20, 2006.

The '892 patent, which issued on July 30, 2002, and is assigned to Alza, contains claims that are directed to a "method of obtaining analgesia in a human patient" by the electrotransport delivery of a dose of fentanyl or sufentanil over a predetermined period. The claims of the '892 patent cover the IONSYS™ product. The term of the '892 patent has not been previously extended and is set to expire on June 5, 2015.

II. The PTO improperly applied Federal Circuit precedent.

In its Notice of Final Determination, the PTO relied on the Federal Circuit decision *Pfizer, Inc. v. Dr. Reddy's Labs., Ltd.*, 359 F.3d 1361 (Fed. Cir. 2004) ("*Dr. Reddy's*") to broadly define the term "product" in the context of eligibility under 35 U.S.C. § 156(a) to include a salt, an ester, or a non-salified and non-esterified form of a molecule so that all three forms of a molecule are the same "product" for purposes of patent term extension under section 156. *See* Notice at 2-4 (citing *Dr. Reddy's*, 359 F.3d at 1366). The PTO also distinguished the earlier Federal Circuit decision *Glaxo Operations UK, Ltd. v. Quigg*, 894 F.2d 392 (Fed. Cir. 1990) ("*Glaxo*"), which interpreted the meaning of "product" more narrowly in the context of eligibility for extension under section 156(a)(5). *See* Notice at 5.

The PTO erred in applying the reasoning in *Dr. Reddy's*, instead of the reasoning in *Glaxo*, to its determination of the eligibility of the '892 patent for patent term extension. In fact, both *Dr. Reddy's* and *Glaxo* remain good law, and the reasoning in *Glaxo* governs the facts of this case. And under the reasoning in *Glaxo*, there is no question that the '892 patent is eligible for patent term extension.

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[1] Formally known as the "Drug Price Competition and Patent Term Restoration Act of 1984," Pub. L. No. 98-417, 98 Stat. 1585 (1984) (codified as amended at 21 U.S.C. § 355) ("Hatch-Waxman amendments" or "Hatch-Waxman").

A. *Glaxo* remains binding precedent.

Glaxo interpreted the meaning of "product" in the context of eligibility under 35 U.S.C. § 156(a)(5), the same statutory section at issue in this case. In contrast, the *Dr. Reddy's* decision the PTO cites interpreted "product" as used in 35 U.S.C. § 156(b), an entirely different provision governing enforcement rights. The *Dr. Reddy's* decision thus is not directly applicable to the patent extension application here.

Federal Circuit Rule 35 explicitly states that "only the court en banc may overrule a binding precedent." The settled law of the Federal Circuit makes clear that a second panel may not overrule a first panel and that it is consequently legal error to read a later decision of a Federal Circuit panel as overruling a decision of an earlier panel. *Barclacy et al. v. U.S.*, 443 F.3d 1368, 1373 (Fed. Cir. 2006) ("Panels of this court are bound by previous precedential decisions until overturned by the Supreme Court or by this court en banc."); *Kimberly-Clark Corp. v. Fort Howard Paper Co.*, 772 F.2d 860, 863 (Fed. Cir. 1985) ("Counsel is apparently unaware that a panel of this court is bound by prior precedential decisions unless and until overturned *en banc*.").

Because *Dr. Reddy's* was a panel decision, it could not have overruled the prior panel decision of *Glaxo*. Rather, *Dr. Reddy's* must be read as compatible with *Glaxo*. This makes sense: *Glaxo* deals with the question of eligibility for patent term extension. *Dr. Reddy's* deals with the different question of, once a patent term has been extended, what products are covered. All told, *Glaxo* remains binding precedent and applies to eligibility for patent term extension, the issue in the present case.

B. Under *Glaxo*, patent term extension of the '892 patent should be granted.

A patent eligible for patent term extension must meet five eligibility requirements: (1) the patent term must not yet have expired; (2) the patent term must not previously have been extended; (3) a patent extension application must be submitted; (4) the product claimed by the patent and/or the product whose use is claimed by the patent must have been subject to a regulatory review period prior to commercial marketing or use; and (5) (with certain exceptions for recombinant DNA processes and new animal drugs or veterinary biologics) the particular commercial marketing or use must be the first such marketing or use of the product permitted by the governing statute. *See* 35 U.S.C. § 156(a).

It is undisputed that four of these five requirements are satisfied in this case. First, the '892 patent has not yet expired. Second, the patent has not previously been extended. Third, the application for the patent term extension of the '892 patent was submitted to PTO within 60 days of FDA approval of the NDA for IONSYS™. Finally, the NDA for IONSYS™ was subject to regulatory review prior to its commercial marketing or use.

The only requirement in dispute is whether IONSYS™, as a combination drug-device that uses a fentanyl hydrochloride precursor to produce protonated fentanyl that is then delivered through the skin by electrotransport, represents the first permitted commercial marketing or use of the approved "product." *See* 35 U.S.C. § 156(f); 37 C.F.R. 1.710.

The meaning of "product" according to the analysis used in *Glaxo* should guide the PTO's decision here. This case concerned Glaxo's request, based on FDA's approval of Glaxo's drug Ceftin, for extension of its patent claiming cefuroxime axetil (an ester of cefuroxime), the active ingredient in Ceftin. The PTO had denied this request on the grounds that Ceftin was not the first approved commercial marketing or use of the "product" in light of the previous approval of two Glaxo drugs, Zinacef and Kefurox (two salts of cefuroxime). The PTO asserted that the definition of "product" should be read to encompass any "'new chemical entity,' *i.e.*, 'new active moiety,' which would encompass all acid, salt, or ester forms of a single therapeutically active substance even if the drug before being administered contained only other substances." *Glaxo*, 894 F.2d at 394. The court in *Glaxo* specifically rejected this argument, and instead focused on the plain language of the statute and determined that the words therein (*i.e.*, "active ingredient," "salt," and "ester") should be held to their ordinary, common meaning. *Id.* at 395. Thus, the court held that the term "drug product" means the drug's active ingredient (including salts and esters thereof), as opposed to a broader definition including any "new chemical entity" or "new active moiety." *See id.* at 400.

In its rejection of Alza's application for patent term extension of the '892 patent, the PTO essentially repeated the losing arguments it made in *Glaxo*, that is, for eligibility, the term "active ingredient" means "active moiety," *i.e.*, "the molecule or ion responsible for the physiological or pharmacological action of the drug, excluding those appended portions of the molecule that cause the drug to be an ester or salt." Notice at 3. Thus, according to the PTO, a patent term extension can only be given to either a salt, an ester, or a non-salified and non-esterified form of a molecule.

Under *Glaxo*, however, each form of the active ingredient is a separate "product" for purposes of eligibility under 35 U.S.C. § 156(a). Fentanyl hydrochloride – a form different from the fentanyl free base found in the previously-approved DURAGESIC system – is the ingredient that exists in the reservoir of the approved IONSYS™ product, and it is this ingredient that serves as the starting material to produce the protonated fentanyl that is electrotransported through the skin. Because neither fentanyl hydrochloride itself nor any other salt or ester of fentanyl hydrochloride previously has been approved, the PTO should extend the '892 patent under the rational of *Glaxo*.[2]

Following the rationale of the Federal Circuit's decision in *Glaxo*, patent term extension is available for subsequent development of a new salt, even if the free base has previously been approved. The reasoning of *Glaxo*, that development of a new salt form may require considerable work and innovation, is clearly true here, where the development of the

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[2] FDA has approved NDAs for the ingredient fentanyl citrate prior to its approval of IONSYS™. *See* Orange Book listing for fentanyl citrate, *available at* http://www.accessdata.fda.gov/scripts/cder/ob/docs/tempai.cfm. This prior approval does not affect the analysis under *Glaxo*. Fentanyl citrate is neither a salt nor an ester of fentanyl hydrochloride. Thus, because neither fentanyl hydrochloride itself nor any salt or ester of fentanyl hydrochloride previously has been approved, the PTO should extend the '892 patent under the rationale of *Glaxo*.

product using the fentanyl hydrochloride precursor was necessary to development of the IONSYS™ system. In this respect, the present invention is entirely unlike those orally administered drug products where the particular salt or ester form of the drug used has little or no effect on the achieved efficacy.

III. Even under the standard articulated by the PTO, the patent term should be extended under the unique facts of this case.

A. Protonated fentanyl, not fentanyl hydrochloride, is the moiety administered to the patient.

In its Notice of Final Determination, the PTO explains section 156(f)(1) defines the term "product" (as used in section 156(a)) as "a drug product." A "drug product" means "the active ingredient of a new drug . . . including any salt or ester of the active ingredient . . . ." 35 U.S.C. § 156(f)(2). Relying on the Federal Circuit's opinion in *Dr. Reddy's*, the PTO concludes that the term "active ingredient" in section 156(f)(2) is synonymous with "active moiety." Notice at 3. And, according to the PTO, active moiety means "the molecule or ion excluding those appended portions of the molecule that cause the drug to be an ester, salt . . . responsible for the physiological or pharmacological action of the drug substance." *Id.* (citing *Dr. Reddy's*, 359 F.3d at 1366). Thus, the PTO concludes that fentanyl is the underlying molecule in both IONSYS™ and DURAGESIC™. "Fentanyl is simply formulated differently in these different drugs: as fentanyl itself in DURAGESIC™, and as the hydrochloride salt of fentanyl in IONSYS™." Notice at 4.

This description of the IONSYS™ system fails to take into account, however, the process of delivery of the IONSYS™ system, which results in a different active moiety being administered to the patient. Upon initiation of administration of the IONSYS™ system, fentanyl hydrochloride is ionized *in situ* to form protonated fentanyl (among other things). This protonated fentanyl is what then crosses the skin of the patient in order to deliver palliative care to that patient.

The '892 patent makes clear that the fentanyl hydrochloride is only the precursor, and the protonated fentanyl is the actual moiety that is delivered to the patient. As the '892 patent notes in its specification, an iontophoretic device militates in favor of using as precursors compounds, such as salts, that easily ionize, to facilitate the process of creating the new compounds that will be administered to patients . *See* '892 specification, col. 1, ll. 55-58 and col. 6, ll. 26-30. In addition, the '892 specification identifies the hydrochloride form of fentanyl as being preferable to other salts as a precursor because it would allow for the formation of "substantially insoluble" compounds when combined with the silver ions that invariably come through the application of a current through the IONSYS™ silver anodes when the protonated fentanyl is created. *Id.* at col. 9, l. 65 to col. 10, l. 12. Other areas of the specification likewise point to the desirability of having a hydrochloride form of fentanyl or sufentanil as the precursor. *Id.* at col. 7, ll. 11-15. But the patent makes clear that it is ions such as protonated fentanyl, not their salt precursors, that are the moiety that is ultimately delivered to the patient.

In addition, the NDA for the IONSYS™ product makes clear that protonated fentanyl, and not fentanyl hydrochloride, is the moiety delivered to the patient. As the NDA

explains, "[t]ransdermal electrotransport of fentanyl is enhanced when fentanyl is in a cationic form." NDA 21-338, Section 2.1.3.1 (Anode Hydrogel Development). When fentanyl hydrochloride is added to water, it ionizes, forming positive fentanyl cations and negative chloride ions. These chloride ions are then available in "the formulation to react with silver cations generated electrochemically during use, forming a layer of [silver chloride] on the surface of the silver anode." *Id.*

Thus, the conclusion that IONSYS™ and DURAGESIC™ share fentanyl as the active moiety is incorrect. Instead, the active moiety in IONSYS™, which is administered to the patient, is protonated fentanyl. Protonated fentanyl is not a salt or ester of fentanyl. FDA has not approved another product that delivers protonated fentanyl for therapy or treatment. Thus, even if the PTO applies its definition of the term "active ingredient" based on its interpretation of *Dr. Reddy's*, patent term extension should be granted because protonated fentanyl has not been previously approved. Accordingly, the IONSYS™ system represents the first permitted commercial marketing or use of the "product" for purposes of section 156(a).

B. Patent term extension of the '892 patent clearly serves the purpose of section 156.

There is a second reason why the PTO should have granted the term extension for the '892 patent, even under the standard offered by the PTO in light of its interpretation of *Dr. Reddy's*. The IONSYS™ product is not simply a drug product. Instead, IONSYS™ is a fentanyl iontophoretic transdermal system, which is a completely new drug-device combination. As explained in the approved labeling for the IONSYS™ system,

> Each IONSYS™ system is composed of a plastic top housing that contains the battery and electronics, and a red plastic bottom housing containing two hydrogel reservoirs and a polyisobutylene skin adhesive. Only one of the hydrogels (the anode, located under the dosing button) contains fentanyl HCl, along with inactive ingredients. The other hydrogel (the cathode) contains only pharmacologically inactive ingredients. The bottom housing has a red tab that is used only for system removal from the skin and during disposal . . . . A siliconized clear, plastic release liner covers the hydrogels and must be removed and discarded prior to placement on the skin. The system is powered by a 3-volt lithium battery.[3]

The '892 patent describes an invention that involves the use of a device for the administration of compounds for palliative care. The invention of the '892 patent is described in the abstract as an "electrotransport drug delivery system for analgesic drugs, namely fentanyl and

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[3] *See* Approved label for IONSYS™ (May 22, 2006), *available at* http://www.fda.gov/cder/foi/label/2006/021338lbl.pdf.

sufentanil." '892 patent abstract. In the "Technical Field" section of the specification, the patent states that "the invention relates to ***a device, composition and method*** for improved electrotransport delivery of analgesic drugs." '892 patent, col. 1, ll. 14-16 (emphasis added). The "Description of the Invention" asserts, "The present invention provides ***a device*** for improved transdermal electrotransport delivery of fentanyl and analogs of fentanyl." '892 patent, col. 4, ll. 65-67 (emphasis added). Finally, the specification sums up the invention as follows, "In summary, the present invention provides ***a device*** for improving the transdermal electrotransport of water soluble salts of fentanyl or sufentanil." '892 patent, col. 13, ll. 44-46.

The claims of the '892 patent similarly make clear that the invention is a device intended to deliver a drug for palliative care. Claim 1, for example, reads as follows:

> A method of obtaining analgesia in a human patient who is suffering from pain, consisting of transdermally delivering solely by electrotransport a dose of about 20μg to about 60 μg of fentanyl over a predetermined delivery period. . .

The '892 patent envisions the use of a device ("transdermally delivering solely by electrotransport") and a drug ("a dose of about 20μg to about 60 μg of fentanyl") for palliative care ("obtaining analgesia"). Thus, the '892 patent, which reads on IONSYS™, intended to cover an innovative drug-device combination and not just a drug product.

Thus, developing the IONSYS™ product was not merely a question of making minor modifications to the DURAGESIC® fentanyl product. Instead, developing the IONSYS™ product involved much research to determine which analgesic compound could work with the innovative electronic method of administration. Ultimately, it was determined that a different active ingredient working through a different mechanism to provide therapeutic benefit to a patient in need had to be used. Although the FDA is reviewing the IONSYS™ system under section 505(b) of the FDCA, the different precursor ingredient (fentanyl hydrochloride) and delivered moiety (protonated fentanyl) reflect the innovation involved in the new drug-device combination.

The development of new and innovative therapeutic products lies at the heart of the Congressional purpose for Title II of the Hatch-Waxman amendments. Congress recognized that federal premarketing and premanufacturing regulations caused the average effective patent term of therapeutic products such as drugs and devices to decline and that a continuation of the decline could result in decreased expenditures for research and development and eventually, in a decline in the introduction of new therapeutic products. H.R. Rep. No. 98-857, pt. 1, at 17 (1984). Thus, as compensation for the loss of patent term due to extensive government review and as a significant incentive to develop new, innovative products, Congress passed section 156. *Id.*; *see also* Statement of Representative Waxman, Cong. Rec. H8706, Aug. 8, 1984 (recognizing that the Hatch-Waxman amendments would "create a significant incentive for the development of new products"). This is precisely the case here, as the invention of the '892 patent could not be marketed until undergoing lengthy FDA review. It is entirely contrary to the

purpose of the statute to deny patent term restoration to a drug-device combination because its active ingredient had previously been approved for delivery in different forms, alone or in combination with entirely different systems.[4] Accordingly, the particular commercial marketing or use of the invention of the '892 patent is indeed the first such marketing or use of the product permitted by the governing statute. *See* 35 U.S.C. § 156(a). As such, patent term restoration is entirely warranted in this case.

Respectfully submitted,

Dated: May 6, 2008

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[4] Under *Glaxo* each form of the active ingredient is a separate "product" for purposes of eligibility under 35 U.S.C. § 156(a).